

Dysphonia and laryngopharyngeal reflux

Disfonia e reflusso faringolaringeo

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Parole chiave

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Summary

The correlation between laryngo-pharyngeal reflux and dysphonia has been evaluated in patients without significant laryngoscopic findings and without vocal misuse. Studies were performed, using a validated questionnaire on typical reflux symptoms as well as instrumental means, e.g. videolaryngoscopy, multi-electrode 24-hr oesophageal pH monitoring, vocal acoustic analysis, gastro-oesophagoscopy, on 62 patients (51 male, 11 female) with dysphonia for ≥ 3 months, selected from 350 consecutive patients presenting with voice disorders. Standard criteria were: absence of laryngeal neof ormation (benign or malignant) and correct use of voice. Anti-reflux treatment was prescribed in all selected patients. A group of 62 selected patients without laryngo-pharyngeal disease were studied as controls. Mean values of the harmonic to noise ratio and maximum phonation time were pathological in all patients with dysphonia and significantly correlated ($p=0$) with the entity of the larynx alteration. The 24-hour pH monitoring revealed gastro-oesophageal reflux in all cases with a clear prevalence of episodes in the upright, compared to supine, position. From a multiple regression analysis of pH-metric values, considered important in predicting maximum phonation time and harmonic to noise ratio alteration, the significant predictors ($p<0.01$) were those parameters indicating the existence of a laryngopharyngeal reflux disease: in an upright position, the prevalence of the number of refluxes and of time of $pH<4$. In conclusion, the association between electro-acoustic reliefs and laryngoscopic data, as well as an alteration in maximum phonation time and harmonic to noise ratio in patients with pH-metric indicative parameters of laryngo-pharyngeal reflux disease led to the hypothesis of a possible correlation between entity and duration of the reflux and dysfunction of the arytenoid muscles, upon which chronic vocal fatigue, with consequent laryngeal compensatory stress, depends.

Riassunto

È stata studiata la correlazione che può esistere tra il reflusso faringolaringeo e la disfonia in quei pazienti che non presentano significativi reperti obiettivi a livello laringeo e non mostrano comportamenti di abuso vocale. Attraverso l'utilizzo di un questionario validato sui tipici sintomi da reflusso e di appositi esami strumentali, come la videolaringoscopia, l'indagine pH-metrica multielettrodo nelle 24 ore, l'analisi elettroacustica della voce, la esofagogastroscoopia, gli Autori hanno studiato 62 pazienti (51 maschi, 11 femmine) che soffrivano di disfonia per almeno 3 mesi precedenti alla visita, selezionati tra 350 pazienti visti consecutivamente per disturbi della voce. I criteri standard di selezione sono stati l'assenza di neof ormazioni laringee (benigne o maligne) ed un corretto uso della voce. A tutti i pazienti è stato prescritto un trattamento antireflusso. Come gruppo di controllo, gli Autori hanno selezionato 62 pazienti senza disturbi faringolaringei. Per tutti i pazienti con disfonia i valori medi di H/N (Harmonic/Noise) e TMF (Tempo Massimo Fonatorio) sono risultati patologici e correlati significativamente ($p=0$) con l'entità delle alterazioni laringee. La pH-metria multielettrodo delle 24 ore ha documentato in tutti i casi l'esistenza del reflusso gastroesofageo, con una chiara prevalenza degli episodi che si verificavano in posizione eretta rispetto a quelli in posizione supina. Dall'analisi di regressione multipla dei parametri pH-metrici ritenuti importanti nel predire le alterazioni del TMF e H/N è emerso che le variabili maggiormente correlate sono state quelle indicative dell'esistenza di un reflusso faringolaringeo: il numero di reflussi e il tempo di $pH<4$ in posizione eretta. Concludendo, l'associazione tra rilievi elettroacustici e segni laringoscopici così come le alterazioni del TMF e H/N nei pazienti con parametri pH-metrici indicativi di reflusso faringolaringeo porta ad ipotizzare una correlazione tra l'entità e la durata del reflusso e la disfunzione dei muscoli aritenoidi, dalla quale dipende un comportamento di sforzo vocale cronico con conseguente stress laringeo compensatorio.

Introduction

Gastro-oesophageal reflux (GER), described as retrograde movements of gastric contents, can induce lesions in the mucosal lining of the oesophagus and, sometimes,

of the laryngo-pharynx, which is not suitable for the presence of the acid, pepsin, pancreatic enzymes.

Over the last few years, much attention has been focused on the extra-oesophageal manifestations of gastro-oesophageal reflux disease (GERD) ¹⁻¹², throwing

further light on the principal (epidemiologic, physiopathologic, clinical-diagnostic and therapeutic) aspects. Indeed, as emerges from the literature¹³⁻¹⁶, alongside the classical and well-defined GERD, a new clinical entity is being delineated, i.e., laryngo-pharyngeal reflux disease (LPRD) which is often independent of GERD and the typical symptoms (heartburn, acid regurgitation, epigastric pain). In fact, recent epidemiologic data^{1 2 7 14 15 17 18} suggest that LPRD plays an aetiopathogenetic role in 10-25% of the patients examined for voice disorders. These symptoms - vocal fatigue, hoarseness, need to clear the throat, globus pharyngeus - in, as yet, not well-defined percentages, may be associated with objective patterns, such as oedema and hyperaemia of the arytenoid cartilage and interarytenoid area, salivary stagnation in the piriform sinus, vocal nodules, vocal fold oedema (simple LPRD) or granulomatous lesions of the posterior glottis, subglottic stenosis, precancerous lesions and carcinoma of the larynx (complicated LPRD). Nevertheless, since, in many cases, organic or functional lesions of the larynx are not detected, the otolaryngologist and phoniatrician often find dysphonia cases of difficult diagnostic definition, in which the medical treatment and the vocal rehabilitation, sometimes, fail to give satisfactory results.

Aim of the present investigation was to evaluate the correlation between LPR and dysphonia, with particular reference to those cases without laryngeal neoformations (benign or malignant) and without vocal misuse.

Patients and methods

From July 2001 to December 2002, studies were carried out on 62 subjects (51 male, 11 female, age range 32-62 years), with dysphonia of at least 3 months duration, selected from 350 patients consecutively observed for voice disorders at the Department of Otorhinolaryngology of the University "Federico II", Naples (Italy).

Selection criteria were as follows:

- no evidence of vocal misuse;
- no neoformations (benign or malignant) detected at laryngoscopy.

None of the patients were taking drugs known to alter oesophageal motor function or gastric acid secretion. Moreover, none had a history of alcohol abuse, diabetes mellitus, vascular or neurologic disease.

The following data were collected for each patient:

1. validated questionnaire, consisting of a list of questions concerning upper airway symptoms specific for pathological reflux (Gastro-oesophageal Reflux Data Sheet) with a 0 to 3 score (0=no symptoms; 3=severe)¹⁹;
2. laryngeal endoscopy: patients underwent video-

laryngoscopic examination with a rigid telescope (Storz 8706 CJ, 90°) connected to video equipment (camera: Atmos K2 with Super VHS video recorder Panasonic AG-7350; monitor: Sony CVM-1810E). Two experienced phoniatricians examined the videotape. Special attention was focused on the posterior wall of the glottis and piriform sinus;

3. vocal acoustic analysis with examination of harmonic to noise ratio (H/N - normal value >7 dB) and maximum phonation time (MPT - normal value >18 sec) (CSL 4400 B, Kay elementics), extracted from 2 central seconds of a sustained phonation of a vowel, using a condenser microphone at a distance of 30 cm from the mouth, at an angle of 45° and sampling rate of 20 KHz;
4. gastro-oesophagoscopy with an Olympus endoscope connected to a Super VHS video recorder Panasonic AG-7350 and monitor Sony CVM-1810E;
5. oesophageal pH monitoring: the subjects underwent 24-hour dual-probe pH monitoring, with 3 monocrystalline antimony pH sensors positioned along a single catheter (Synectis Medical Inc., diameter 2.1 mm). One was positioned in the gastric cavity, another 5 cm above the lower oesophageal sphincter (LES), identified by the rapid pull-through method, and the third, 15 cm from the second. Mean duration of the examination was 23.16±1 hours and, during the recording, the subjects were encouraged to eat their regular meals with restriction of coffee, alcohol, acid substances and smoking. Data were examined using a Version 5.70C2 EsopHgram from Gastrosoft Inc. Patients were considered negative for pathological proximal reflux when showing <10 episodes of reflux, with percent total time to acid exposure (pH <4) <0.5%, and complete absence of reflux in the supine position (Table I). For distal reflux, the number of episodes of reflux per hour in a supine position, upright position and post-prandial phase, as well as the percent time of mucosal exposure to acid pH (pH <4) were taken into consideration (Table II)¹⁹⁻²¹. All patients kept a detailed diary indicating the time of oral intake, change in position (upright and supine), and symptomatic events, such as regurgitation.

Table I. Normal value of proximal reflux.

pH variables	Total	Supine position
Reflux episodes (n)	<10	0
Percentage time pH <4	<0.5	0
Average time (min)	<2.1	0

Table II. Normal value of distal reflux.

pH variables	Total	Upright position	Supine position	Postprandial
Reflux episodes/h (n)	<2.09	<2.98	<0.87	<3.83
Percentage time pH <4	<4.74	<4.95	<2.20	<10.80
Average time (min)	<1.30	<0.90	<1.51	<1.69
Time pH <4 (min)	<36	<33	<4.20	

* Significant association ($p < 0.01$) between the pH variables and position of patient (upright, supine) or meals (during or after) (ANOVA).

Antireflux treatment was prescribed for all selected patients, using an acid-suppressive agent, omeprazole (proton pump inhibitor or PPI) 40 mg b.d., for two consecutive months.

At the end of the treatment, patients were re-examined including videolaryngoscopy and vocal acoustic analysis.

As controls, we consecutively selected 62 patients, matched for age, sex, smoking, and alcohol habits, referred to our ENT outpatient clinic for non-laryngopharyngeal diseases. All control patients completed the same above-mentioned examinations.

The data were analysed using the SPSS 7.0 statistics package²². All results are mean $\pm$ SD. Statistical analysis was performed using Student t test to define improvements resulting from the medical treatment. Differences between the groups of patients as far as concerns MPT and H/N, pre- and post-treatment, and the variations in pH monitoring values, according to the position of the patients, were evaluated by analysis of variance (ANOVA). A multiple regression analysis was performed to establish which pH monitoring values were important in predicting alterations in MPT and H/N.

For the statistic reliability, a value of $p < 0.01$ has been chosen.

Institutional Review Board approval was obtained and all patients gave consent to take part in the study.

Results

As far as concerns the group with dysphonia, 4 patients (2 male, 2 female) failed to complete the diagnostic-therapeutic trial. Prior to medical treatment, the majority of these patients (55=94.8%) complained of vocal fatigue and hoarseness; in 31 patients (53.4%) globus pharyngeus, need to clear the throat and excess mucus, were also found; 4 patients (6.9%) presented dysphagia for liquids. Only in 23 patients (39.6%) were heartburn and epigastric pain, typical of GERD, also found, proving that pharyngo-oesophageal reflux may be present without typical symptoms.

It was possible, following laryngeal endoscopy, to divide patients with dysphonia into three distinct groups (Table III):

- Group A: 31 patients (53.4%, 26 males, 5 females, mean age 49.8 years) presenting with light oedema and hyperaemia of the arytenoid cartilage and interarytenoid area;
- Group B: 8 patients (13.9%, 6 males, 2 females, mean age 54.4 years) with evident oedema and thickening of the arytenoid and interarytenoid region;
- Group C: 19 patients (32.7%, 17 males, 2 females, mean age 52.3 years) in whom the only objective finding was salivary stagnation in one or both piriform sinuses.

As far as concerns the vocal acoustic analysis (Table III), mean values of the parameters examined (H/N and MPT) were pathological for all the groups with dysphonia, with significant differences ($p=0$) between them, and were correlated to the entity of the larynx alteration at videolaryngoscopy (group B>group A>group C).

Gastro-oesophagoscopy revealed hiatus hernia in 6 cases (2 in group A, 3 in group B, 1 in group C) and small oesophageal diverticulum in 2 patients (1 in group A, 1 in group B).

The 24-hour oesophageal pH monitoring of patients with dysphonia (Table IV) showed values in excess of normal limits, indicative of pathological reflux, in all 58 cases with a clear prevalence of episodes in the upright, compared to the supine, position.

ANOVA of the pHmetric results showed a significant correlation ($p < 0.01$) between the parameters evaluating the entity and duration of the reflux (number of episodes, longest episode, time pH<4) and the position of the patient (upright, supine) or the meals (during or after); the parameters evaluated showed the greatest alterations in the upright position.

After antireflux treatment, the symptoms improved in 43 cases (74%) with a corresponding remission of the objective findings at laryngoscopy and of the acoustic parameters at spectrography (Table V). In fact, in these patients, a regular distribution of harmonics, in

Table III. Laryngoscopic and spectrographic findings before treatment.

Group	Patients n. (%)	Laryngeal findings	Vocal acoustic analysis	
			MPT (sec)* (range)	H/N (dB)* (range)
Group A	31 (53.4%)	Light oedema and hyperaemia of the arytenoid cartilage and interarytenoid area	13.55±0.63 (12.2-14.9)	1.57±0.39 (0.9-2.3)
Group B	8 (13.9%)	Evident oedema and thickening of arytenoids and interarytenoid region	12.01±0.32 (11.2-13)	-1.53±0.32 (-2.2--0.5)
Group C	19 (32.7%)	Salivary stagnation either in one or both piriform sinuses	14.2±0.68 (13.20-15.80)	3.18±0.96 (1.40-4.80)

* Significant difference between groups for MPT ($F=4.89$, $p=0$) and H/N ($F=4.89$, $p=0$) parameters (ANOVA); MPT: maximum phonation time; H/N: harmonic to noise ratio.

Table IV. Median oesophageal 24-hour pH monitoring values.

pH variables	Total	Upright position	Supine position	During meal	Postprandial
Reflux episodes (n)*	154.60±66.61	134±61.87	19.80±14.94	21.60±14.40	62.80±38.19
Long reflux (n)	3.40±2.79	2±1.87	1.80±1.92	0.20±0.45	1±0.71
Longest episode (min)*	27±12.86	25.20±13.99	12.60±10.92	1.60±2.07	12.60±10.92
Time pH <4 (min)*	122.80±56.46	84.20±44.85	37.80±27.96	7.60±7.89	49.60±27.86
Percentage time pH <4*	8.72±3.93	12.36±7.26	8.24±6.29	8.74±9.02	9.14±4.71

* Significant association ($p<0.01$) between pH variables and position of patient (upright, supine) or meals (during or after) (ANOVA).

the entire spectrum and a significant increase in the MPT and H/N indexes, compared to the period prior to the medical therapy ($p=0$), were observed.

Furthermore, the absence of significant differences, between the 3 groups, was clearly visible, both for the MPT ($F=4.93$, $p=0.83$) and for the H/N ($F=4.93$, $p=0.92$).

Finally, from a multiple regression analysis of pH-metric parameters considered important in predicting changes in MPT and H/N, significant predictors ($p<0.01$) were the number of reflux episodes in the upright position, the time pH <4 (min) in the upright position, the percentage time pH <4 in the upright position and the postprandial time at pH <4 (Tables VI, VII).

In the control group, it was seen, from the validated questionnaire, that none of the patients complained of reflux symptoms. Laryngoscopy was normal in all patients, while oesophageal pH monitoring showed pathological reflux episodes in 9 out of 62 (14.5%) patients. Compared to the group with dysphonia, a significant difference was observed in the percentage of reflux episodes that reached the pharynx ($p<0.01$).

Discussion

LPRD is a disease that, today, on account of the physiopathological, clinical-diagnostic and therapeutic characteristics, directly, involves the ENT specialist. Indeed, many studies have recently appeared in the literature^{3 4 6 7 9 10 12-15 23} aimed at establishing the onset, clinical manifestations and therapeutic aspects of this condition.

Data acquired on the physiopathologic mechanisms, from which LPR causes diseases/disorders of the ENT districts, seem to indicate that a prominent role is played by the damaging effect of the acid complex on the pharyngolaryngeal mucosa. Stomach acid operates either by a direct mechanism or indirectly by stimulation of the parasympathetic terminations present in the mucosal lining of the oesophagus with triggering of the cough reflex and consequent trauma of the glottis. Indeed, although the frequency and the time of exposure to the acid material affects the intensity of the pathological pictures also in the pharyngolaryngeal tract, it is important to bear in mind that, unlike the oesophagus, the upper aereo-digestive tract is

Table V. Laryngoscopic and spectrographic findings, after treatment.

Groups	Patients n (%)	Remission of laryngeal findings n (%)	Vocal acoustic analysis MPT (sec)* (range)	H/N (dB)* (range)
Group A	31 (53.4%)	24 (77.4%)	17.97±1.69 [†] (15-21)	6.78±1.27 [†] (4.10-9.20)
Group B	8 (13.9%)	6 (75%)	18.26±0.99 [†] (15.50-21)	6.84±0.49 [†] (4.80-7.60)
Group C	19 (32.7%)	13 (68.4%)	17.98±1.40 [†] (15-21)	6.90±1.16 [†] (4.20-9.20)

* No difference between groups for MPT (F=4.93, p=0.73) and H/N (F=4.93, p=0.92) parameters (ANOVA); [†] The difference in each group pre- and post-therapy is statistically significant: p=0 (Student-t test); MPT: maximum phonation time; H/N: harmonic to noise ratio.

Table VI. Multiple regression analysis of pHmetric variables – predictors of MPT changes*.

pHmetric variables	Parameter estimate	p value
Reflux episodes in upright position	0.97	0.002
Time pH <4 in upright position	0.77	0.009
Percentage time pH <4 in upright position	0.86	0.009
Time pH <4 in postprandial period	0.90	0.008

* Data refer to pre-treatment period.

Table VII. Multiple regression analysis of pHmetric variables - predictors of H/N changes*.

pHmetric variables	Parameter estimate	p value
Reflux episodes in upright position	0.87	0.009
Time pH <4 in upright position	0.73	0.008
Percentage time pH <4 in upright position	0.74	0.008
Time pH <4 in postprandial	0.77	0.009

* Data refer to pre-treatment period.

sensitive to the damaging action of even small quantities of the reflux, as if deprived of effective anti-reflux mechanisms (such as mucosal secretions and constant bathing in basic saliva). While the oesophagus succeeds in neutralizing those physiological episodes of reflux, the pharyngo-laryngeal district is extremely vulnerable to peptic damage, that can occur at every single episode of reflux, especially in the presence of an already inflamed mucosa due to concomitant inflammatory episodes of the upper aereo-digestive tract.

Moreover, recent studies^{1 13 17 18 24-27} performed with 24-hour oesophageal pH monitoring have revealed some peculiar aspects of LPRD, not present in GERD,

such as the prevalence of the diurnal reflux and in an upright position, contributing to differentiate these two pathological forms.

Finally, as far as concerns an analysis of therapeutic trials^{7 12 16 27}, the percentages of resistance (20-40%) to established medical treatment (PPI 40 mg per day, in two administrations, for 6 months) do not, at present, allow a well-standardized therapeutic protocol to be set up, unlike the classical GERD; therefore, large randomized placebo-controlled trials are required to clarify this aspect.

In the present study, the incidence of LPRD (16.5%), in the patients attending our Unit for voice disorders, is in keeping with percentages reported in the litera-

ture^{7 14 15 17 18}, according to which LPRD would play a significant role in 10-25% of the voice disorders; instead, in our patients with LPRD and laryngeal symptoms, the presence of laryngeal findings clearly appears inferior, compared to the literature. In fact, only in 13.9% of our patients was evident oedema and hypertrophy of the arytenoid and interarytenoid region, compared to 40% of patients in other studies^{7 14 15 17 18}. In the remaining 86.1%, there was a poor and non-specific objectivity to laryngoscopy (in 31 patients, a light oedema and hyperaemia of the arytenoid cartilage and interarytenoid area, in 19 subjects, salivary stagnation in one or both piriform sinuses), thus attributing a predominant role to the history. Furthermore, in the present study, LPRD occurred in 14.5% of the healthy controls, which is almost equal to the previously reported prevalence of 16-26%^{1 25}. In accordance with other Authors^{7 12-15 17}, a low percentage of patients (39.6%) has been found who complained of the classical symptoms of GERD, even if the endoscopic findings had always excluded the presence of oesophagitis, and had only documented hiatus hernia in 10.3% of the subjects and oesophageal diverticulum in 3.4% of the cases. These data seem to confirm the findings of Moller et al.¹⁸, according to whom the absence of typical symptoms cannot exclude clinical supra-oesophageal manifestations related to GER.

As far as concerns vocal acoustic analysis, the parameters MPT and H/N, before treatment, were significantly correlated ($p=0$) with the severity of the laryngoscopic findings, with the most severe modifications being found in cases of pronounced oedema and hypertrophy of the arytenoid and interarytenoid region. These two parameters (MPT and H/N) showed a significant improvement ($p=0$) in all 3 groups following pharmacological treatment with PPI, especially in the group with a more severely impaired laryngeal picture/condition before medical treatment (group B).

This association between the electro-acoustic and the clinical data led us to consider a possible correlation between the entity and the duration of the reflux and the dysfunction of the arytenoid muscles, upon which reduced phonation time and chronic vocal fatigue depend, with consequent laryngeal compensatory stress. The most significant alterations in MPT and H/N, in group B (patients with prevalent involvement of the posterior wall of the glottis), would indicate the need to reevaluate the role of the posterior laryngitis in the pathogenesis of the dysphonia, which often appears to go unnoticed in the literature¹⁸. In fact, the posterior portion of the larynx, due to the anatomical proximity to the oesophagus, is more exposed and more sensitive to the irritating effect of acid reflux.

With the aid of 24-hour pH monitoring, we have been able to document the episodes of GER, in all patients,

analysing the characteristics of distribution and duration as well as the modality of realization. Indeed, we have been able to clearly record a larger number of GER episodes in the upright, compared to the supine position (134 vs 19.8, $p<0.01$) according to other Authors^{1 13 17 18 24-27}, with pH time <4 , in this position, being significantly greater ($p<0.01$): these data decrease the therapeutic role of correct posture, during the night hours, to prevent episodes of LPR.

The multiple regression analysis confirms that indicative pH monitoring values of LPRD (prevalence of reflux in the upright position, longer pH <4 time, in this position) were significant predictors ($p<0.01$) of MPT and H/N deterioration and thus of a greater alteration in the laryngeal picture.

Conclusions

Data emerging from the present study confirm the estimated LPRD incidence reported in the literature (16.5%) in patients seeking attention for voice disorders, without neoformations (benign or malignant) at laryngoscopy; on the other hand, in our patients with LPRD and laryngeal symptoms, the presence of laryngeal findings appears inferior compared to reports in the literature. In fact, only in 13.9% of our patients, was evidence of oedema and hypertrophy of the arytenoid and interarytenoid region found, compared to 40% of patients in other studies. In 86.1%, there was a poor and non-specific objectivity at laryngoscopy: this stresses the importance of the history in this condition. The data emerging from the vocal acoustic analysis showed a significant correlation ($p=0$) between the severity of the voice disorders and the importance of the laryngoscopic findings, and, furthermore, underline an alteration in the electro-acoustic reliefs in patients with pHmetric parameters indicative of LPRD: for this reason, it is mandatory to reevaluate the role of GER/LPR in the pathogenesis of dysphonia, since this could, during a superficial examination, appear dysfunctional. Thus oesophageal 24-hour pH monitoring, in the presence of dysphonic symptoms showing no improvement following common therapies, becomes an important diagnostic tool also in those cases with a negative history for GER/LPR. The systematic search for RFL in dysphonia with a negative clinical objectivity would not only contribute to a more correct epidemiologic and diagnostic classification but also the possibility to define a more precise medical approach thus avoiding the need for patients to undergo prolonged cycles of anti-inflammatory therapy or phoniatric rehabilitation, which are often completely ineffective.

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